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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,715	07/18/2003	Toshihiro Mori	2870-0258P	1567

2292 7590 12/21/2005

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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/621,715	MORI ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-20-2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

The description of Fig. 5 (p.7) could be made clearer by indicating the source of the material for each lane of the agarose gel photograph depicted in Fig. 5. For example: 'lane (2) – DNA from the nucleic acid mixture recovered from a 50% saponified membrane with pore size 0.2μm (condition (b) from p.29)'.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1, 11, 14 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Qiagen (1999a) as evidenced by Qiagen (1999b).

3. Qiagen (1999a) teaches a method capable of separating nucleic acids of different lengths from a nucleic acid mixture. The reference teaches the use of Qiagen Resin (which is an organic macromolecule having hydroxyl groups as indicated by the structure of the resin displayed in Fig.1, p.2 of Qiagen (1999b)), which binds nucleic acid molecules directly correlated to their charge densities (p.3, right column). The size dependent separation of nucleic acids by the Qiagen resin is indicated in Fig 3 (p.4). The reference also teaches the use of a medium salt wash to remove contaminants,

and elution of DNA with a high salt buffer (p.3, right column), relevant to claim 14, which creates the limitation of using a washing buffer and a desorbing liquid. Figure 7 (p.6) of the reference teaches that the Qiagen resin can be held in a syringe-like 'tip', with a loading opening on the top and a elution opening on the bottom, relevant to claim 17 which creates the limitation of using a unit for separation having at least two openings that contains the solid phase organic macromolecule.

4. This rejection cites two references. However, the second reference (Qiagen 1999b), is cited as it provides evidence of the inherent characteristics of the Qiagen Resin disclosed in Qiagen 1999a, specifically that the resin is an organic macromolecule having a hydroxyl group on the surface thereof (MPEP 2131.01).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 11, 14, and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,187,083 in view of US Patent 6,056,877.

With regard to claim 1, the '083 patent teaches a method comprising the steps of adsorbing a nucleic acid onto a solid phase composed of an organic macromolecule having a hydroxyl group on a surface thereof, and desorbing the nucleic acid from the solid phase (Example 1, Col. 7-8).

Specifically, the '083 patent teaches the capture and elution of DNA from blood on cellulose acetate membrane filters (Col. 7, line 45), which are organic macromolecules. Cellulose acetate inherently has hydroxyl groups on the surface thereof.

With regard to claim 11, the nucleic acid is in a sample solution (a lysis solution of human blood; Col. 7, lines 34-40).

With regard to claim 14, the '083 patent teaches washing the solid phase with a nucleic acid washing buffer after adsorbing and then desorbing the nucleic acid from the solid phase with a solution capable of desorbing the nucleic acid from the solid phase. Specifically, the filter is washed with SDS/PBS solution and Tris chloride after adsorption (Col. 7, lines 46-51), and then the nucleic acid is desorbed using another aliquot of Tris chloride (Col. 7, lines 54-57).

With regard to claim 16, the desorbing solution has a salt concentration of 0.5 M or less (Col. 7, lines 54-55).

With regard to claim 17, the '083 patent teaches an example wherein the adsorption and desorption of the nucleic acid is performed within a vacuum-filtration device which is a container with at least two openings and which contained a cellulose acetate membrane filter, which is a solid phase composed of an organic macromolecule having a hydroxyl group on a surface thereof (Example 3).

With regard to claim 18, the '083 patent teaches a method wherein adsorption and desorption of the nucleic acid is performed by use of a unit for isolation and purification comprising (a) a solid phase of the organic macromolecule having a

hydroxyl group on the surface thereof; (b) a container having at least two openings and containing the solid phase; and (c) a differential pressure generator connected to one opening of the container. Specifically, the '083 patent teaches an example wherein the adsorption and desorption of the nucleic acid is performed within a vacuum-filtration device which is a container with at least two openings and which contained a cellulose acetate membrane filter, which is a solid phase composed of an organic macromolecule having a hydroxyl group on a surface thereof (Example 3). Further, the vacuum filtration device would inherently be connected to a differential pressure generator (i.e. the vacuum) that is connected to an opening of the device.

The '083 patent does not teach the separation of a nucleic acid having a predetermined length from a nucleic acid mixture.

The '877 patent teaches media and methods for polynucleotide separations. The reference teaches that polynucleotides of different predetermined lengths can be separated from a nucleic acid mixture by adsorbing and desorbing (referred to in the '877 patent as applying and eluting) a mixture of nucleic acids to a solid phase separation media (col.3 lns.9-16; Example 8). The reference indicates that separation particles and polymers may consist of a variety of different substances, and specifically mentions the use of cellulose (col.3, lns.40-55).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the nucleic acid purification method of the '083 patent so as to have used it for the separation of nucleic acids by size as exemplified by the method of the '877 patent. One would have been motivated

to combine these methods based on the attractive DNA binding characteristics of cellulose acetate as described in the '083 patent and the assertion of the '877 patent that chromatographic separation methods of nucleic acids are important because of their amenability to automation (col.1, ln.41), and because the '877 patent suggests the use of cellulose as a separation polymer (col.3 ln.50; col.5 ln.25).

7. Claims 1, 11, 12, and 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0512767 in view of US Patent 6,056,877.

With regard to claim 1, EP 0512767 teaches a method comprising the steps of adsorbing a nucleic acid onto a solid phase composed of an organic macromolecule having a hydroxyl group on a surface thereof, and desorbing the nucleic acid from the solid phase (p. 3, lines 19-30 and Example 6, p. 9).

Specifically, EP 0512767 teaches the capture and elution of DNA from samples onto hydrophilic surfaces including nitrocellulose (p. 3, lines 49-50), which is an organic macromolecule that inherently has hydroxyl groups on the surface thereof.

With regard to claim 11, the nucleic acid is in a sample solution (p. 4, lines 7-10).

With regard to claim 12, EP 0512767 teaches a steps of treating a sample containing a cell or a virus with a nucleic acid solubilizing reagent (i.e. a lysis buffer) and then preparing the sample solution by adding an aqueous organic solvent to the solution. Specifically, EP 0512767 teaches that DNA is obtained in such a way that the procedure ends with a suspension of DNA in a solution such as a lysate, a step which inherently includes treating the sample with a solubilizing reagent (p. 3, lines 3-13). EP

0512767 teaches the subsequent addition of an organic solvent to the solution (p. 3, lines 19-22).

With regard to claim 14, EP 0512767 teaches washing the solid phase with a nucleic acid washing buffer after adsorbing and then desorbing the nucleic acid from the solid phase with a solution capable of desorbing the nucleic acid from the solid phase. Specifically, EP 0512767 teaches a step referred to as the "wash step" and suggest wash buffers (p. 3, lines 24-25), and that the nucleic acid is desorbed using an elution buffer (p. 3, lines 27-28).

With regard to claim 15, EP 0512767 teaches the nucleic acid washing buffer that contains 50% ethanol, for example (p. 3, line 24).

With regard to claim 16, the desorbing solution has a salt concentration of 0.5 M or less (p. 3, lines 27-28).

With regard to claims 17 and 18, EP 0512767 teaches the use of a unit for isolation and purification that has a container with two openings that contains the solid phase and is attached to a differential pressure generator; specifically, the use of a blotter which "pulls liquid through a membrane (p. 9, lines 5-15).

EP 0512767 does not teach the separation of a nucleic acid having a predetermined length from a nucleic acid mixture.

The '877 patent teaches media and methods for polynucleotide separations. The reference teaches that polynucleotides of different predetermined lengths can be separated from a nucleic acid mixture by adsorbing and desorbing (referred to in the '877 patent as applying and eluting) a mixture of nucleic acids to a solid phase

separation media (col.3 lns.9-16; Example 8). The reference indicates that separation particles and polymers may consist of a number of different substances, and specifically mentions the use of cellulose (col.3, lns.40-55).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the nucleic acid purification method of EP 0512767 so as to have used it for the separation of nucleic acids by size as exemplified by the methods of the '877 patent. One would have been motivated to combine these methods based the DNA purifying ability of nitrocellulose as described in EP 0512767 and the assertion of the '877 patent that chromatographic separation methods of nucleic acids are important because of their amenability to automation (col.1, ln.41), and because the '877 patent suggests the use of cellulose as a separation polymer (col.3 ln.50; col.5 ln.25).

8. Claims 1-6, 10-12, and 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0512767 in view of US Patent 4,118,336, and US Patent 6,056,877.

With regard to claims 1, 11, 12, and 14-18, this rejection is written to address the embodiment of these claims wherein the polymer is surface-saponified cellulose acetate.

With regard to claim 1, EP 0512767 teaches a method comprising the steps of adsorbing a nucleic acid onto a solid phase composed of an organic macromolecule

having a hydroxyl group on a surface thereof, and desorbing the nucleic acid from the solid phase (p. 3, lines 19-30 and Example 6, p. 9).

Specifically, EP 0512767 teaches the capture and elution of DNA from samples onto hydrophilic surfaces including nitrocellulose (p. 3, lines 49-50), which is an organic macromolecule that inherently has hydroxyl groups on the surface thereof.

With regard to claim 11, the nucleic acid is in a sample solution (p. 4, lines 7-10).

With regard to claim 12, EP 0512767 teaches a steps of treating a sample containing a cell or a virus with a nucleic acid solubilizing reagent (i.e. a lysis buffer) and then preparing the sample solution by adding an aqueous organic solvent to the solution. Specifically, EP 0512767 teaches that DNA is obtained in such a way that the procedure ends with a suspension of DNA in a solution such as a lysate, a step which inherently includes treating the sample with a solubilizing reagent (p. 3, lines 3-13). EP 0512767 teaches the subsequent addition of an organic solvent to the solution (p. 3, lines 19-22).

With regard to claim 14, EP 0512767 teaches washing the solid phase with a nucleic acid washing buffer after adsorbing and then desorbing the nucleic acid from the solid phase with a solution capable of desorbing the nucleic acid from the solid phase. Specifically, EP 0512767 teaches a step referred to as the "wash step" and suggest wash buffers (p. 3, lines 24-25), and teaches that the nucleic acid is desorbed using an elution buffer (p. 3, lines 27-28).

With regard to claim 15, EP 0512767 teaches the nucleic acid washing buffer that contains 50% ethanol, for example (p. 3, line 24).

With regard to claim 16, the desorbing solution has a salt concentration of 0.5 M or less (p. 3, lines 27-28).

With regard to claims 17 and 18, EP 0512767 teaches the use of a unit for isolation and purification that has a container with two openings that contains the solid phase and is attached to a differential pressure generator. Specifically, EP 0512767 teaches the use of a blotter which "pulls liquid through a membrane (p. 9, lines 5-15).

EP 0512767 does not teach a method wherein the macromolecule is surface-saponified acetylcellulose acetate or surface-saponified triacetlycellulose.

With regard to claims 2 and 3, the '336 patent teaches surface saponified cellulose diacetate and triacetate particles and suggest using these for purification of nucleic acids (Col. 9, lines 6-7; Col. 9, line 16; Col. 10, line 7).

With regard to claims 4 and 5, the '336 patent teaches surface saponified cellulose acetate particles wherein the saponification rate is 10% or more. For example, turning to example 1, the acetylation degree before saponification was 54.1% but less than 0.4% after saponification (Col. 9, lines 35-36).

With regard to claim 6, the cellulose layer on the microparticles is inherently a porous film.

With regard to claim 10, the cellulose acetate is coated on microcapsules, which are beads.

In addition, with regard to claim 17 the '336 patent exemplifies the use of the particles packed into a column, a structure that inherently has two openings.

Niether EP 0512767 nor the '336 patent teach the purification of a nucleic acid of predetermined length. The '877 patent teaches media and methods for polynucleotide separations. The reference teaches that polynucleotides of different predetermined lengths can be separated from a nucleic acid mixture by adsorbing and desorbing (referred to in the '877 patent as applying and eluting) a mixture of nucleic acids to a solid phase separation media (col.3 lns.9-16; Example 8). The reference indicates that separation particles and polymers may consist of a number of different substances, and specifically mentions the use of cellulose (col.3, lns.40-55).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the surface saponified cellulose triacetate taught by the '336 patent and the nucleic acid purification methods taught by EP 0512767 with the polynucleotide separation methods taught by the '877 patent. One would have been motivated to use the particles taught by the '336 patent in the separation methods taught by EP 0512767 in view of the teachings EP 0512767 that binding matrixes suitable for use in their invention include any hydrophilic surface (specifically mentioning particles as an option (p. 3, lines 49-52)). The '336 patent provides such a surface, and specifically suggest the use of the surface for the extraction and purification of nucleic acids (Col. 9, lines 6-7). It would have been further obvious to use these methods and reagents for the separation of nucleic acids by size as exemplified by the methods of the '877 patent, which asserts that methods of chromatographic separation of nucleic acids are important because of their amenability to automation (col.1, ln.41), and specifically mentions the use of cellulose as a

separation polymer. Therefore, in view of the teachings of EP 0512767 , the '336 patent, and the '877 patent, the claimed invention is *prima facie* obvious.

9. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0512767 in view of US Patent 6,056,877 as applied to claims 1, 11, 12, and 14-18 above, and in further view of US patent 5,695,946; or as being unpatentable over EP 0512767 in view of US Patent 4,118,336, and US Patent 6,056,877 as applied to claims 1-6, 10-12, and 14-18 above, and in further view of US Patent 5,695,946.

The teachings of EP 0512767 in view of the '877 patent are applied to claim 13 as they are previously applied to the rejection of claims 1, 11, 12, and 14-18 previously in this office action.

Alternatively, the teachings of EP 0512767 in view of the '336 patent and the '877 patent are applied as they are applied in the rejection of claims 1-6, 10-12, and 14-18 previously in this office action.

EP 0512767 teaches using "typical" procedures for obtaining DNA from samples (p. 3, lines 5-6). Neither EP 0512767 in view of the '877 patent, nor EP 0512767 in view the '336 patent and the '877 patent, teach a step wherein the nucleic acid solubilizing reagent comprises a guanidine salt, a surfactant, and a proteolytic enzyme.

The '946 patent teaches that target nucleic acid molecules are released from cells by treatment with any number of reagents, including guanidine salts, proteinase K and detergents (Col. 8, lines 7-12). The '946 patent exemplifies the use of the surfactant SDS for cell lysis (Col. 12, line 15).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by EP 0512767 in view of the '877 patent, or EP 0512767 in view the '336 patent and the '877 patent, so as to have utilized a lysis buffer that included reagents that are typically considered lysis agents for the release of nucleic acids from sample cells. One would have been motivated by the teachings of EP 0512767 that any such typical methodologies for obtaining lysis solutions could be used and by the teachings of the '946 patent that each of these reagents are commonly used for the lysis of cells.

10. Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0512767 in view of US Patent 6,056,877 as applied to claims 1, 11, 12, and 14-18 above, and in further view of WO 99/13976; or as being unpatentable over EP 0512767 in view of US Patent 4,118,336, and US Patent 6,056,877 as applied to claims 1-6, 10-12, and 14-18 above, and in further view of WO 99/13976.

The teachings of EP 0512767 in view of the '877 patent are applied to claim 13 as they are previously applied to the rejection of claims 1, 11, 12, and 14-18 previously in this office action.

Alternatively, the teachings of EP 0512767 in view of the '336 patent and the '877 patent are applied as they are applied in the rejection of claims 1-6, 10-12, and 14-18 previously in this office action.

Neither EP 0512767 in view of the '877 patent, nor EP 0512767 in view of the '336 patent and the '877 patent, teach the sequence of steps required in claims 19 and

20 wherein fluids are brought into contact with the solid support by inserting one opening of a unit for isolation and purification into a fluid (first sample, second washing buffer, third desorbing solution), creating a reduced pressure in a container by a differential pressure generator to suck the fluid into the chamber and into contact with the hydroxyl group, and creating an increased pressure within the chamber which results in discharge of the fluid from the chamber. Claim 19 requires the repetition of these steps for three different fluids, while claim 20 requires the repetition of these steps for only the sample and the desorbing solution.

WO 99/13976 teaches methods for isolation of nucleic acid from samples and teaches automated steps of loading a sample into a container with at least two openings (p. 7, lines 11-12), loading a wash into the container (p. 7, lines 13-17), and loading desorbing buffer (referred to as elution buffer) into the container (p. 7, lines 18-23). WO 99/13976 teaches the use of vacuum pumps for the movement of solutions into and out of the isolation chamber (p. 8, lines 6-14; 21-22). WO 99/13976 specifically teach that methods in which the sample is loaded via aspiration which occurs via the insertion of the opening of the chamber into the sample and the application of negative pressure to suck the sample into the chamber (p. 10, exemplified p. 23). Further, WO 99/13976 teaches methods in which the gases are pumped into the chamber which increases pressure in the chamber and forces fluid out of the chamber (p. 12, lines 13-15).

Thus, in view of the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the methods taught by EP 0512767 in view of the '877 patent, or EP 0512767 in view the '336 patent and the '877

patent, to include the sample processing methodologies taught by WO 99/13976. One would have been motivated to apply the methods of WO 99/13976 to the methods taught by EP 0512767 in view of the '877 patent, or EP 0512767 in view the '336 patent and the '877 patent, in order to have provided methods for applying the fluids necessary to practice the methods taught by EP 0512767 to the solid supports for the isolation of nucleic acids.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some amount of separation of a 1.3kb DNA fragment from a 48kb DNA fragment in a mixture containing said DNA fragments, using surface saponified triacetlycellulose, does not reasonably provide enablement for the separation of any sized nucleic acid fragments from one another from within a mixture containing any number and type of nucleic acid fragments of differing lengths using any organic macromolecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The nature of the invention is a method for separating and purifying a nucleic acid of a predetermined length from a mixture of nucleic acids using solid phase organic macromolecule, and more specifically using a porous membrane consisting of surface saponified triacetlycellulose. Alteration of the surface saponification rate of acetylcellulose and the size of the pores in a film made from the compound allows for the adsorbing of particularly sized nucleic acids, and their subsequent purification by desorbing. The nature of the invention requires knowledge of the relationship of the surface saponification rate of organic macromolecules and film pore size with recovery rate of any particular length of nucleic acid.

The claims encompass the separation and purification of any type of nucleic acid (e.g. DNA or RNA) from a nucleic acid mixture of any complexity (i.e. containing any amount of nucleic acids of any length). Claims 1 and 11-20 encompass the use of any organic macromolecule having hydroxyl groups. Claims 2, 3, 6, 7 and 10 encompass the use of any surface saponification rate; and claims 4 and 5 encompass the use of any surface saponification rate higher than 5% or 10%, respectively. Claim 8 encompasses the use of any surface saponification rate with any pore size; and claim 9 encompasses the use of any surface saponification rate higher than 10% and any pore size between 0.1μm and 10μm.

State of the prior art, level of skill, and level of unpredictability

While the level of skill in the art of nucleic acid separation is high, the state of the prior art with regard to nucleic acids binding to acetylcellulose indicates a high level of unpredictability. The prior art does not teach any correlation between particular

saponification rates or pore sizes and the ability of an organic macromolecule to separate nucleic acids of specific lengths from mixtures of nucleic acids.

Several references teach that cellulose acetate membranes will not bind to DNA. GE Osmonic (1997) teaches the use of cellulose acetate membranes to filter nucleic acid probes, indicating the membrane is ideal because it is a non-DNA binding polymer. Similar statements about cellulose acetate are taught in two recent references: Corning (2005) indicates that cellulose acetate is inert, and does not bind either DNA or protein, and Whatman (2005) indicates that ability of DNA to bind to cellulose acetate is 'very low'.

It is also unpredictable how the sequence of any particular DNA might affect its ability to be separated in a size dependant manner using the methods described by the instant specification. Yang et al (1998) teach that DNA molecules with particular sequences (Table 1, p.5465) can bind tightly and specifically to cellulose. It would therefore be unpredictable how the presence of any of the indicated 'cellulose-binding DNA aptamer' sequences, within a larger nucleic acid sequence, would affect the separation of the nucleic acid by the method of the instant application regardless of the saponification rate or pore size of a medium containing an organic macromolecule with hydroxyl groups.

Van Oss et al (1987) indicate the unpredictability of different nucleic acids (e.g. DNA versus RNA) binding to acetylcellulose. The reference teaches that while interaction between DNA and cellulose esters can be considerable, the binding energy of RNA to cellulose esters is low (p.53). Table IV (p.60) indicates the clear difference in

free energy of adhesion of DNA on cellulose acetate versus RNA on cellulose acetate; the reference teaches that DNA should bind more strongly to cellulose esters that RNA (p.61), and RNA is much more weakly attracted to cellulose esters than DNA (p.63). Pan et al (2003) teaches the inherently different structural properties of DNA versus RNA. The reference indicates that different chemistries of DNA and RNA allow for different flexibilities and the adoption of different conformations, thus making it unpredictable as to how these different molecules would interact with the membranes (i.e. varying saponification rates and pore sizes) discussed in the instant application.

Direction provided and presence of working example

The instant specification asserts that nucleic acids can be separated and purified by preparing a plurality of porous membranes with varying surface saponification rates and varying pore sizes. The specification provides data regarding the recovery rate of two DNA fragments (1.3kb and 48kb) from various preparations of triacetylcellulose (p.28, Tables 3 and 4; Fig 5). The specification teaches that recovery rate (that is the percentage of the DNA that is applied to a membrane which is adsorbed to the membrane and then desorbed from the membrane) varies between two different saponification rates (either 50% or 100%) and four different pore sizes (0.2, 0.4, 1.0, or 2.5μm). There is no other information provided for any other saponification rates or pore sizes. Notably, there is no information contained within the specification for saponification rates lower than 50% (as are encompassed by the claims, for instance claims 4 and 5 which particularly point out saponification rates with lower limits of 5% and 10%, respectively). Similarly, there is no other information provided for any pore

size other than those listed in Table 1; notably there is no information in the specification concerning pore sizes larger than 2.5μm (as are encompassed by the claims, for instance claim 9 which particularly points out pores sizes as large as 10μm).

The specification indicates (pp.10-11) the following saponification rates combined with the following pore sizes will allow the recovery (by adsorbing and subsequently desorbing) of particularly sized DNA: both low molecular weight DNA and high molecular weight DNA were recovered from 100% saponified membranes with 0.2μm pores; recovery of high molecular weight DNA is relatively higher (compared to recovery of low molecular weight DNA) from 50% saponified membranes with 0.2μm pores; the recovery rate of high molecular weight DNA is high from 100% saponified membranes with 2.5μm pores.

The specification provides a single example of the purification of a low molecular weight nucleic acid and a high molecular weight nucleic acid from a nucleic acid mixture (pp.28-29). This example demonstrates the separation of a 1.3kb fragment from a 48kb fragment which had been mixed together in an aqueous solution. In the example, the different DNAs are separated by the sequential action of a first membrane (100% saponified, 0.2 μm pore size) and a second membrane (50% saponified, 0.2 μm pore size). And while the specification asserts that it is clear from the results of Fig. 5 (a photograph of an agarose gel) that a nucleic acid having a desired size can be purified by selecting saponification rate and pore size, there is no quantification of the results to indicate the resulting level of separation. For instance, regarding the isolation of the 1.3kb DNA (condition (c) on p.29) from a mixture containing 10μg each of a 1.3kb DNA

and a 48kb DNA (as in (4) on p.27), one would expect (based on the collection rate information presented in Tables 3 and 4) for the final recovered product to contain 7.7µg of 1.3kb DNA and 1.4µg of 48kb DNA.

The specification does not provide any example of the separation of any other nucleic acid mixtures other that the 1.3kb and 48kb mixture described in Example 1, or results concerning recovery rates from any other saponification rates or pore sizes than those presented in Tables 3 and 4. It is unknown what resolution of separation would be attainable with other membrane and/or nucleic acid mixture conditions. For instance, are there any possible conditions that would allow for the separation of a 9kb DNA fragment from an 11kb DNA fragment. Additionally, while the specification refers to conditions for purification of high molecular weight versus low molecular weight molecules, the specification refers to a 10kb fragment as both a relatively long nucleic acid (p.12 ln.1) and a relatively short nucleic acid (p.12 ln.11).

The specification does not provide any guidance concerning the separation of any nucleic acid mixtures containing anything other than the double stranded DNA of Example 1.

Quantity of experimentation required

A prohibitive amount of experimentation would be required to use the claimed invention in its full scope. For any given mixture of nucleic acids, one would have to establish the recovery rate of a nucleic acid of interest having a particular length under different saponification and pore size conditions. One would also have to determine if

the described methods would be compatible RNA, or perhaps with other types of nucleic acids such as peptide nucleic acids (PNA).

Alteration of saponification rate alone would require a large quantity of experimentation. The specification indicates conditions used to achieve either 50% or 100% saponification (p.26), however there is no way to predict what conditions are needed to achieve any other saponification rates (e.g. what concentration of sodium hydroxide solution to use, and how long to treat a membrane). The specification only indicates that altering sodium hydroxide concentration can change saponification rate (p.10), and that the rate is determined by quantifying remaining acetyl groups by NMR.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and scope of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the lack of a working examples, it is the conclusion the an undue amount of experimentation would be required to use the invention in the full scope of the claims.

13. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification has not taught how to make a non-porous surface saponified acetylcellulose membrane as required by claim 7. Cellulose acetate membranes,

inherently, are porous membranes. The specification does not provide any working examples of non-porous cellulose acetate membranes. It would require inventive and undue experimentation in order to determine how to provide such a non-porous surface saponified cellulose acetate membrane for the practice of the claimed invention since none are known to exist. Therefore, it is concluded that it would require undue experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 and 10-20 are indefinite in the recitation 'separating and purifying a nucleic acid having a predetermined length' in the preamble of the claim. The claims merely state the method step of absorbing and desorbing nucleic acid to and from a solid phase organic macromolecule, and do not include how the a specific nucleic acid of predetermined length is in fact separated from the nucleic acid mixture; hence the method steps do not correlate with the preamble, and it is unclear how the claimed method accomplishes the purpose of the method.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of copending Application No. 10/305,110. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '110 application recite a method comprising the same steps as the method of the instant application, specifically absorbing and desorbing nucleic acid to and from a solid phase material containing hydroxyl groups. Because the method of the copending claims recite the relevant features of the rejected claim, they would inherently be capable of accomplishing the intended use of the rejected claim as detailed in the rejected claim, specifically separating and purifying a nucleic acid having a predetermined length.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 1-7 and 10-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 10/621,329. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '329 application recite a method comprising the same steps as the method of the instant application: absorbing and desorbing nucleic acid to and from a solid phase material containing hydroxyl groups, specifically surface saponified acetylcellulose, the use of solubilization reagents, washing and desorbing buffers, and particular separation units and steps for contacting nucleic acids with a purification medium. Because the methods of the copending claims recite the relevant features of the rejected claims, they would inherently be capable of accomplishing the intended use of the rejected claims as detailed in the rejected claims, specifically separating and purifying a nucleic acid having a predetermined length.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 1-7 and 10-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 10/621,412. Although the conflicting claims are not

identical, they are not patentably distinct from each other because the claims of the '412 application recite a method comprising the same steps as the method of the instant application: absorbing and desorbing nucleic acid to and from a solid phase material containing hydroxyl groups, specifically surface saponified acetylcellulose, the use of solubilization reagents, washing and desorbing buffers, and particular separation units and steps for contacting nucleic acids with a purification medium. Although claim 1 of the '412 application does not specify hydroxyl groups on the surface of the organic macromolecule, subsequent claims specify acetylcellulose, which inherently contains hydroxyl groups. Because the methods of the copending claims recite the relevant features of the rejected claims, they would inherently be capable of accomplishing the intended use of the rejected claims as detailed in the rejected claims, specifically separating and purifying a nucleic acid having a predetermined length.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Claims 1-7 and 10-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 10/209,336. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '336 application recite a method comprising the same steps as the method of the instant application: absorbing and desorbing nucleic acid to and from a solid phase material containing hydroxyl groups, specifically surface saponified acetylcellulose, the use of

solubilization reagents, washing and desorbing buffers, and particular separation units and steps for contacting nucleic acids with a purification medium. Because the methods of the copending claims recite the relevant features of the rejected claims, they would inherently be capable of accomplishing the intended use of the rejected claims as detailed in the rejected claims, specifically separating and purifying a nucleic acid having a predetermined length.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 1-7 and 10-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-34 of copending Application No. 10/808,411. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '411 application recite a method comprising the same steps as the method of the instant application: absorbing and desorbing nucleic acid to and from a solid phase material containing hydroxyl groups, specifically surface saponified acetylcellulose, the use of solubilization reagents, washing and desorbing buffers, and particular separation units and steps for contacting nucleic acids with a purification medium. Because the methods of the copending claims recite the relevant features of the rejected claims, they would inherently be capable of accomplishing the intended use of the rejected claims as detailed in the rejected claims, specifically separating and purifying a nucleic acid having a predetermined length.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claims 1-7 and 10-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of copending Application No. 10/932,138. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '138 application recite a method comprising the same steps as the method of the instant application: absorbing and desorbing nucleic acid to and from a solid phase material containing hydroxyl groups, specifically surface saponified acetylcellulose, the use of solubilization reagents, washing and desorbing buffers, and particular separation units and steps for contacting nucleic acids with a purification medium. Although claim 1 of the '138 application does not specify the separation medium, subsequent claims (e.g. claim 17) specify saponified triacetyl cellulose, which inherently contains hydroxyl groups. Because the methods of the copending claims recite the relevant features of the rejected claims, they would inherently be capable of accomplishing the intended use of the rejected claims as detailed in the rejected claims, specifically separating and purifying a nucleic acid having a predetermined length.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. Claims 1-7 and 10-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 10/975,469. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '469 application recite a method comprising the same steps as the method of the instant application: absorbing and desorbing nucleic acid to and from a solid phase material containing hydroxyl groups, specifically surface saponified acetylcellulose, the use of solubilization reagents, washing and desorbing buffers, and particular separation units and steps for contacting nucleic acids with a purification medium. Although claim 1 of the '138 application does not specify the separation medium, subsequent claims (e.g. claim 20) specify saponified triacetyl cellulose, which inherently contains hydroxyl groups. Because the methods of the copending claims recite the relevant features of the rejected claims, they would inherently be capable of accomplishing the intended use of the rejected claims as detailed in the rejected claims, specifically separating and purifying a nucleic acid having a predetermined length.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

23. No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached at 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PRIMARY EXAMINER